AstraZeneca

Date: AUG 01 2005

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0062
Response to FDA Call for Comments
"FDA's 'Drug Watch' for Emerging Drug Safety Information"

Dear Sir or Madam:

Reference is made to the May 10, 2005 Federal Register notice announcing the request for comments on "FDA's 'Drug Watch' for Emerging Drug Safety Information."

AstraZeneca has reviewed this notice and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Barry Sickels, Executive Director, at (302) 886-5895.

Sincerely,

Anthony F. Rogers
Vice President
U.S. Regulatory Affairs
Telephone: 302-886-2127
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MM/bm

Enclosure

2005D-0062

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Draft Guidance for Industry on the Food and Drug Administration's "Drug Watch" for Emerging Drug Safety Information

[Docket No. 2005D-0062]

General Comments:

We appreciate the FDA's effort, through the "Drug Watch" for Emerging Drug Safety Information (Drug Watch), to provide meaningful risk information to patients and providers in an easily accessible manner. In order for Drug Watch to be the most helpful and effective initiative, however, it is important that: (1) there be a high, transparent, and consistent threshold for placing a drug on Drug Watch, (2) the underlying information be scientifically sound, (3) Drug Watch not be used by competing manufacturers as basis for comparative safety claims, (4) FDA emphasize to patients and providers in a meaningful manner that Drug Watch information is extremely preliminary, the data is raw, and further (scientific) evaluation is necessary, (5) FDA make a clear statement to patients/consumers that all drugs have risks and those risks must be appropriately weighed and balanced against the potential benefits for a particular patient or particular population of patients. It is also important to note that when risks are known, they can often be managed effectively so as to maximize the benefit and minimize the potential risk to patients.

There must be a high, transparent, and consistent threshold for placing a drug on Drug Watch. The Agency needs to provide more detail and clarity as to the type of information that will be posted on Drug Watch and what triggers a posting. The guidance generally states that FDA will post information on *significant* emerging safety issues FDA is evaluating, but significant is not defined. There is a potential that the general public will be unnecessarily alarmed over a potential safety issue, especially since FDA states they will post information before they have fully investigated. In addition, the posting of a potential safety issue will likely generate an increase in reporting of adverse events, many unsubstantiated (both related and unrelated to the specific issue) directly to both sponsors and FDA by patients and healthcare professionals.

The Draft Guidance does not make clear whether FDA will post only marketed drugs on Drug Watch or whether it will also include post marketed drugs in development for a new indication. This should be specifically addressed in the Guidance. Similarly, the Guidance does not address whether FDA, when posting information relating to a potential signal relating to one drug in a class, will perform an analysis and preliminary assessment relating to other drugs in the class. This is important, as physicians shouldn't switch patients from one treatment to another within the same class, thinking there is less risk, if the risk may be a class effect. There also appears to be no process, or timeframe, for removing a Drug Watch listing. Accordingly, a listing on the proposed Drug Watch should appear for no longer than 90 days before it is removed by either a formalized label change or a Health Alert notification that formally addresses the safety concern for the original posting, or by a formally documented decision that there is no merit to the information to warrant further formal posting on the web site and that no serious health risk exists from the data that was posted.

The potential safety risk(s) noted on Drug Watch must be supported by sound scientific data. The posting of information on Drug Watch based on an active AERs investigation is disconcerting inasmuch as it is a fairly low threshold for an Agency imprimatur on an unsubstantiated issue. In addition, it raises the question of whether the mere filing of a Citizens Petition or the FDA's investigation of a Citizens Petition, based on AERs, would be sufficient to have a drug placed on Drug Watch. Neither the filing, in and of itself, of a Citizens Petition, nor the investigation thereof, should be sufficient to trigger the posting of a drug to Drug Watch.

In general, a better approach may be to post information at the point when there is more sound, substantiated information— perhaps at the point when the agency would notify a sponsor to change its labeling. Providing preliminary information before its significance can be determined seems unnecessarily premature and can discourage the use of a drug in patients who could potentially benefit from it. Such preliminary unsubstantiated information will also have a profoundly negative impact on the drug. Removing a drug from Drug Watch or posting clarifying information will not "un-ring" the bell. Thus, it is important that the FDA use sound and substantial scientific data to trigger a drug's posting to Drug Watch. Providing credible, well-substantiated information at the outset will better serve patients and providers; clarifying or removing information at a later point will be extremely confusing.

The FDA must state clearly, concisely, and prominently on each page of the Drug Watch web site that all drugs have risks and should also make clear that each patient should discuss the benefits and risks with his/her physician for all drugs being taken, not just prescribed drugs.

Finally, the Guidance indicates the Agency *may* notify the sponsor before a drug is posted on Drug Watch. Whether a drug sponsor will be provided with prior notification and the timing of this notification needs to be clarified. Similarly, there should be some ability for the sponsor to respond. Allowing the sponsors of drugs posted to Drug Watch to respond will enable a sponsor to assist the Agency with its evaluation by providing additional information. In addition, it will help the sponsor in responding to patients, health care professionals and others.

In summary, we believe the concept of Drug Watch is admirable and given the proliferation of information, all too often incorrect or misleading, available on the Internet, it is important that the public have a trusted source such as the FDA for information on potential adverse effects of various drugs. However, this information must be provided in a manner that makes clear that all drugs have risks and many of those risks can be managed. Moreover, it is important that Drug Watch not do more harm than good by unnecessarily confusing and/or alarming patients, causing them to overreact and not take medication that can improve their lives. Any communication of information should be meaningful to patients and healthcare professionals. Similarly, it is important that FDA not make it difficult for doctors to prescribe important medications to meet their patients' needs because of fear potential malpractice claims.

Specific Comments:

Section **Number**	Page or Line#	Comment or proposed replacement text
I. Introduction	Line 22	If the industry notifies FDA of important new findings, will those findings be posted to Drug Watch?
I. Introduction	Line 33	Delete uncertainty
II. Background	Lines 64-65	"Our goal with Drug Watch is to share emerging safety information before we have fully determined its significance..." This suggests the information can be preliminary, unsubstantiated, and/or poorly substantiated and yet be the kind of information placed on Drug Watch. We believe FDA should impose a more rigorous standard for the inclusion of information on its Drug Watch.
II. Background		The posting of information based on an active AERs investigation on Drug Watch is disconcerting inasmuch as it is a fairly low threshold for an Agency imprimatur on an unsubstantiated issue. In addition, it raises the question of whether the mere filing of a Citizens Petition or the FDA's investigation of a Citizens Petition, based on AERs, would be sufficient to have a drug placed on Drug Watch.
III. Discussion		Due consideration needs to be given to concomitant diseases, concomitant medication, age and ethnicity. The proposed disclaimer is meant to provide context. However, we know from experience with interpretation of the AERs database, that disclaimers are not appropriately used or understood. Misinterpretation of potential risks could cause patients and clinicians to stop needed treatment, in the absence of an understanding of risk/benefit assessment.
III. A.		"... the Web page will contain factual information about newly observed, serious adverse events associated with the use of a drug..." The word "associated" in this context is somewhat troubling particularly since the example given on lines 85-88 specifically states that "a causal relationship has not been established" (line 86). We believe it is important that FDA note the adverse events observed ***may be*** associated with a particular drug but such association is based on preliminary information. For example, lines 96-97 of the Draft Guidance states, "...the Web page may contain information about significant emerging risks that FDA believes ***may be*** associated with a drug..." The word "associated" has different connotations in the medical, legal and regulatory settings, and could have significant legal implications. See also bullet for lines 137-140

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III. A.	Line 76	Clarify and specify, articulate and define when a drug is posted on Medwatch.
III. A.	76	Definition of significant would be helpful.
III. A.	Lines 80-81	Will FDA notify the sponsor prior to the issue being posted? If it's newly observed, how would a sponsor hear about the issue - a Medwatch (or several); PSUR; clinical data? A minimum timeframe for notifying a sponsor should also be established (e.g. 72 hours).
III. A.	Line 100-101	The example of Drug B seems to reflect a situation that should already be labeled; something this potentially serious should already be known about a drug prior to approval
III. A.	Line 120-124	This is an important point and needs to be made very clear. Part of the disclaimer should include a statement that FDA is working diligently with the sponsor to ensure timely information gathering and resolution of the issue.
III. A.	Line 121	"This information reflects FDA's preliminary analysis." What rises to the level of "preliminary analysis"? Will there be consistent criteria used across the board for all drugs? Again, we believe there should be a higher standard, inasmuch as "preliminary analysis" suggests the data could be raw.
III. A.	Line 126	This paragraph could leave room for confusion and misuse by competing companies.. Please consider highlighting.
III. A.	Line 133-143	Issues can be posted and then removed without clear information on how the issue progressed. FDA should provide clear information on how the matter was resolved and why no safety issue exists.
III. A.	Lines 137-140	"Posting information on Drug Watch Web page does not mean that FDA has concluded there is a causal relationship between the drug product and the risks or adverse events described. Such posting also does not mean FDA is advising practitioners to discontinue prescribing the products that appear on the Drug Watch." While product liability issues are not technically within FDA's mandate, FDA must be sensitive and give consideration to the potentially adverse legal implications a Drug Watch Web page can have. The mere mention of a certain drug on the site could spawn product liability and/or medical malpractice claims notwithstanding adverse events reported may not be borne out as having been associated with a particular drug. AERs have certainly made FDA cognizant that legal actions are often undertaken based on preliminary, unconfirmed information. Thus, it is incumbent upon FDA to have a strong disclaimer statement that includes the language

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		proposed in the Draft Guidance (lines 24-25 and 137-140) **and** language akin to that in 21 C.F.R. 314.80(k) **and** a statement noting the information is very preliminary and there is no need for the manufacturer to pull the drug from market. Even with such disclaimers, however, the legal implications of Drug Watch are tremendous and not easily, if at all, overcome by strong disclaimers. Thus, physicians and other health care professionals may be reluctant to continue prescribing a drug on Drug Watch for fear of being sued for malpractice. We urge FDA, therefore, to give very serious, critical consideration to the potential legal implications and consequences, as well as the potential over-reaction and confusion it could cause patients/consumers.
Footnote 5		How will the "patient information sheets" and "healthcare professional information sheets" differ from manufacturers' labeling? It appears there is the potential for overlap and confusion with regard to which product information is the "official" information. Differences in the way we state information and the way FDA states it could raise legal issues. How should industry handle any differences in these types of documents?
III.E.	Lines 229-240	"Neither the fact that a drug appears on the Drug Watch nor the specific information posted about that drug will generally constitute (either separately or collectively) substantial evidence or substantial clinical experience to support a comparative safety or effectiveness claim..." While this language is important, we do not believe it goes far enough. There is nothing in the Draft Guidance that would prohibit noting in some way that a competitor's product is on Drug Watch. We believe the FDA should make clear that a competitor cannot use such information in print or broadcast advertisements nor have their sales reps mention it when making their sales calls. We would also note that the phrase "generally constitute" on line 235 is ambiguous and should be deleted.